REMARKS

Claims 1-56, 62-65, and 82-86 have been cancelled, new Claims 87-95 have been added, and claims 57, 66 and 75 have been amended. Accordingly, Claims 57-61 and 66-95 are pending. No new matter has been added by this amendment. Applicants respectfully request reconsideration of the application in view of the amendments made herein, and the comments presented below.

DISCUSSION OF REJECTION FOR LACK OF UTILITY

The Examiner rejected Claims 57-61 and 66-83 under 35 U.S.C. §101 and alleges that the claims are drawn to an invention with no apparent or disclosed specific, substantial and credible utility. The Examiner argues that the specification does not disclose a **specific** biological role for the Mrg X protein in nociception, and that one of ordinary skill in the art would not believe that the plurality of receptor proteins described in the application play a common role in nociception. He also argues that the identification of agonists or antagonists have no immediate practical value because the specification does not credibly identify the effects that the administration of an Mrg X agonist or antagonist would have on an organism. The Examiner likened the instant application with the situation in *Brenner v. Manson* wherein the U.S. Supreme Court held that a composition with no practical "real world" value did not meet the statutory requirement of 35 U.S.C. § 101. Applicants respectfully disagree.

The Examiner Has Not Made A Prima Facie Showing To Establish That Applicants' Asserted Screening Utility Is Not Specific Or Substantial

In order to make a *prima facie* showing that the asserted utility is not specific or substantial, the Examiner must establish that it is more likely than not that a person of ordinary skill in the art would not consider Applicants' asserted utility to be specific or substantial. The *prima facie* showing must contain 1) an explanation that clearly sets forth the reasoning used in concluding that the asserted utility for the claimed invention is not both specific and substantial, nor well-established, 2) support for factual findings relied upon in reaching the conclusion, and 3) an evaluation of all relevant evidence of record, including utilities taught in the closest prior art. (*See* Utility Guidelines, 66 Fed. Reg. 1092 (2001) at 1098). For the reasons discussed below,

the Examiner has not established that it is more likely than not that a person of ordinary skill in the art would not consider Applicants asserted screening utility to be specific or substantial.

The Asserted Utility is Specific

A "specific" utility is one that is specific to the subject matter claimed. This contrasts with a general utility that would be applicable to the broad class of the invention. Applicants' disclosed utility relates to the use of a specific receptor to screen for compounds that modulate pain sensation. Compounds modulating pain sensation are determined by their binding to the Mrg receptor (SEQ ID NO: 16). The use of polypeptides having at least 95% sequence identity to SEQ ID NO: 16 in the process for identifying compounds that modulate pain perception is specific for the claimed polypeptides, and not a general technique for all polypeptides. *See* page 9, lines 7-10 of the specification. Compounds are identified, at least in part, by their ability to bind to polypeptides having at least 95% sequence identity to SEQ ID NO: 16.

Accordingly, the asserted utility of determining compounds which modulate pain by binding to the recited polypeptides is specific to those polypeptides and is not applicable to other polypeptides, receptors or even G-protein coupled receptors in general. Thus, one of ordinary skill in the art is more likely than not to find that Applicants' asserted utility is a specific utility.

The Asserted Utility is Substantial

A "substantial" utility is one that defines a real-world use. As provided in the Utility Guidelines, one example of a substantial utility is an assay method for identifying compounds that themselves have a "real-world" use. Evidence of a substantial utility does not require irrefutable proof or identification of an exact function. Rather, a substantial utility only requires a "reasonable" confirmation of a real world context of use (see, e.g., Utility Guidelines, Example 12, Analysis of Claim 1).

Applicants' claims relate to their discovery that Mrg X molecules that were only found on a therapeutically important, and specific sub-population of neurons in the Dorsal Root Ganglia (DRG) were useful to screen for compounds that modulate pain sensation. As is known to those of skill in the art, the DRG is made of a wide variety of cell types. Over 25 functionally diverse populations of cells make up the DRG, each being specialized to encode a variety of sensory events. Some specialized subpopulations of DRG neurons are involved in detection of noxious

sensations, and are termed "nociceptive neurons." Samples of noxious sensations include thermal, chemical or mechanical stimuli that are perceived as pain. Accordingly, nociceptive neurons are also known as "pain-sensing" neurons.

The specification discloses that the Mrg receptors are specifically expressed in $TrkA^+$ nociceptive neurons within the DRG. More specifically, the receptors were only found on in a very particular subclass of nociceptive neurons that bind the lectin IB4 ($IB4^+$) (specification, page 21, lines 30, page 22, line 5, and Figure 20). It was already known in the art at the time of filing that $IB4^+$ neurons are involved in chronic pain transmission (*Caterina and Julius*, Curr. Opinion Neurobiology 9:525-530 (1999), attached herewith). These same $IB4^+$ neurons were also known to be involved in neuropathic pain (*Malmberg et al.* Science 278:279-283 (1997), attached herewith). In addition, Applicants demonstrated that Mrg receptors are activated by several classes of RFamide neuropeptides, which are known to mediate analgesia (Example 5, page 100).

The Examiner, however, argues that the instant claims are drawn to a method of identifying antagonists and agonists of a protein of as yet undetermined biological significance. Applicants strongly disagree. The specification conclusively demonstrates that Mrg polypeptides are G-protein receptors that bind ligands that are known to be involved in pain sensation.

At the time the application was filed, most of the known G protein-coupled receptors expressed on sensory neurons, such as the $IB4^+$ pain sensing neurons, were involved in mediating pain sensation. For example, opioid receptors, cannabinoid receptors, protaglandin receptors, CGRP receptors, serotonin receptors, brandykinin receptors, purine receptors, metabotropic glutamate receptors and NPFF receptors are all G-protein coupled receptors that mediate pain and are expressed on sensory neurons. As demonstrated in Example 5 and Table 4 of the specification, Applicants demonstrated that Mrg receptors bound, and were activated, by several known analgesic compounds, including NPFF.

The results provided in the specification indicating that Mrg receptors are pain signaling molecules were obtained from more than one Mrg family member, were conclusive, were consistent across all family members tested, and have been confirmed by subsequent work in the field. With respect to MrgX1 in particular, Lembo et al. demonstrated that SNSR4, which is greater than 90% identical to MrgX1, is expressed exclusively in human DRG (Nature Neuroscience 5:201-209 (2002), attached herewith). Importantly, Lembo et al. found that cells stably expressing SNSR4 were activated by the opioid-type ligand BAM-22. As a result, based

solely on the results presented in the specification as filed, one of skill in the art would reasonably conclude that the Mrg molecules are G protein-coupled receptors that are expressed in pain sensing neurons in the dorsal root ganglia. Indeed, it is much more likely that a person of ordinary skill in the art would conclude that Applicants' asserted utility is very useful for determining compounds that mediate pain sensation, as fully described in Example 5 of the specification.

As one of skill in the art is more likely than not to conclude that Mrg receptors are pain signaling molecules, the disclosed and demonstrated utility of screening for compounds that mediate pain sensation does not require further research to reasonably confirm a real-world context of use. Compounds that modulate pain sensation, particularly chronic pain and neuropathic pain, have a well-known therapeutic value.

Moreover, Applicants' utility is not analogous the situation in *Brenner v. Manson* (148 U.S.P.Q. 689, 383 U.S. 519 (Sup. Ct. 1966)). In *Brenner*, the U.S. Supreme court found that claims relating to a process for making steroids, wherein the specification asserted no use at all for the final products, did not meet the utility requirement. That is very different from the instant specification which directly teaches that Mrg molecules are receptors which bind compounds, such as NPFF, that are known to affect pain sensation. For all of the above reasons, the Examiner has not made a *prima facie* case that Applicants' asserted utility is neither specific or substantial. Accordingly, Applicants respectfully request withdrawal of this rejection.

Any *Prima Facie* Case Made By The Examiner Has Been Rebutted

Even if a *prima facie* showing of no specific and substantial credible utility has been established, Applicants have successfully rebutted this showing by their arguments and the attached DECLARATION of Dr. Anderson, an inventor of the claimed invention.

While the Applicant bears the burden of rebutting a *prima facie* showing, the Applicant can do this by providing arguments and evidence in the form of a declaration under 37 CFR 1.132 that rebuts the basis or logic of the *prima facie* showing. (1099 Federal Register, Vol. 66, No. 4, Friday, January 5, 2001). The Examiner *must* treat as true a statement of fact made by an Applicant in relation to an asserted utility, unless countervailing evidence can be provided that shows that one of ordinary skill in the art would have a legitimate basis to doubt the credibility of such a statement. (*Id.*) (emphasis added). It is essential for the Examiner to recognize, fully consider and respond to each substantive element of any response to a rejection based on lack of

utility. Only where the totality of the record continues to show that the asserted utility is not specific, substantial, and credible should a rejection based on lack of utility be maintained.

Applicants attach herewith a DECLARATION of one of the inventors, David J. Anderson. In the DECLARATION, Dr. Anderson states that in view of the information provided in the specification as filed, in combination with his knowledge of the state of the art at the time the application was filed, he believed that the claimed receptor, MrgX1, was a G protein coupled receptor involved in pain signaling. It was also his scientific opinion that this receptor was useful for identifying compounds that modulate pain sensation in the body.

The Examiner has provided no countervailing evidence that shows one of ordinary skill in the art would have a legitimate basis to doubt the credibility of Dr. Anderson's statement. Accordingly, accepting this statement as true, one of ordinary skill in the art would believe that the claimed receptor was useful for determining compounds that mediate pain sensation. For this reason, assuming *arguendo*, the Examiner has made a *prima facie* case for lack of utility, Applicants' evidence successfully rebuts the basis for the Examiner's rejection. For this reason, Applicants respectfully request withdrawal of this rejection.

DISCUSSION OF REJECTIONS UNDER 35 U.S.C. §112

The Examiner rejected Claims 57-61 and 66-83 under 35 U.S.C. §112, first paragraph for the same reasons given with regard to the rejections for lack of utility. For all of the reasons discussed above, the claimed invention is supported by a specific, substantial and credible utility. Accordingly, Applicants respectfully request withdrawal of this rejection under 35 U.S.C. §112.

The Examiner also rejected Claims 75-81 and 83 under 35 U.S.C. §112, first paragraph as allegedly failing to comply with the written description and enablement requirements. The Examiner argued that the term "known Mrg polypeptide agonist" was not adequately described. The Examiner asserted that because the specification did not sufficiently describe the required agonist, it fails to provide critical information needed to practice the assay, and to demonstrate Applicants were in actual possession of the invention. Applicants respectfully disagree.

Independent Claim 75 relates to a method for identifying an Mrg polypeptide antagonist by "contacting a host cell known to be capable of producing a second messenger response and expressing an Mrg polypeptide with a known Mrg polypeptide agonist and a candidate antagonist". Referring to Example 5 of the specification, Applicants demonstrate that Mrg

polypeptides are agonists for a variety of ligands, including several known analgesics (Specification, at page 100). Approximately 45 candidate peptides were screened for their ability to activate MrgA1 using an intracellular calcium release assay. Table 4 provides results identifying several agonists that activated this Mrg receptor. Accordingly, the specification fully demonstrates that Applicants were in possession of agonists against Mrg receptors, and that one of ordinary skill in the art would be enabled how to make and use the claimed assay. For this reason, Applicants respectfully request withdrawal of this rejection.

The Examiner rejected Claims 57-61 and 66-83 under 35 U.S.C. §112, second paragraph as being indefinite for employing the term "Mrg polypeptide" as a limitation. While Applicants disagree with the Examiner and point to the specification as describing the metes and bounds of this term, Applicants have amended the claims to recite a molecule having "at least 95% sequence identity to SEQ ID NO: 16". Support for this amendment can be found in the specification at page 4, line 25. For this reason, Applicants respectfully request withdrawal of this rejection.

DISCUSSION OF REJECTIONS UNDER 35 U.S.C. §102

The Examiner rejected Claims 57-61, 66-74 and 82 as allegedly being anticipated by Ahmad et al. (WO 99/32519). The Examiner argues that because the present application is not entitled to priority under 35 U.S.C. §120, the Ahmad reference is prior art against the instant application. Applicants strongly disagree.

As described above, Applicants fully enabled the scope of their claims by teaching how to make and use the claimed invention. In view of the arguments presented above, Applicants submit that the rejection under §101 and the related rejection under 35 U.S.C. §112 are improper. As the utility described in the instant application is also fully disclosed in priority application 09/704,707, Applicants submit that they are entitled to the priority date of this application under 35 U.S.C. §120. As a result, WO99/3519 is not available as prior art under 35 U.S.C. §102(b). For this reason, Applicants respectfully request withdrawal of this rejection.

CONCLUSION

Applicants have endeavored to address all of the Examiner's concerns as expressed in the outstanding Office Action. Accordingly, amendments to the claims, the reasons therefor, and arguments in support of the patentability of the pending claim set are presented above. Any claim amendments which are not specifically discussed in the above remarks are made in order to improve the clarity of claim language, to correct grammatical mistakes or ambiguities, and to otherwise improve the capacity of the claims to particularly and distinctly point out the invention to those of skill in the art. In light of the above amendments and remarks, reconsideration and withdrawal of the outstanding rejections is specifically requested. If the Examiner finds any remaining impediment to the prompt allowance of these claims that could be clarified with a telephone conference, the Examiner is respectfully requested to initiate the same with the undersigned.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: July 12, 2004

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